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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/728,276	12/04/2003	Gregory S. Bisacchi	QA0210 NP	7135
23914	7590	12/14/2005	EXAMINER BERCH, MARK L	
STEPHEN B. DAVIS BRISTOL-MYERS SQUIBB COMPANY PATENT DEPARTMENT P O BOX 4000 PRINCETON, NJ 08543-4000			ART UNIT 1624	PAPER NUMBER
DATE MAILED: 12/14/2005				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/728,276	Applicant(s) BISACCHI ET AL.	
	Examiner Mark L. Berch	Art Unit 1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-24 is/are pending in the application.
 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-24 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>5/10/04</u> . | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6, 8, 10, 13, and 21-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Adlington (1999) and Adlington (2001).

In Adlington (1999), see compound 14. This corresponds to $R_2=R_3=D=H$, zero total A groups (i.e. A=bond), B is phenyl, R1 is C(O)OR7 and X1 is C(O)R7. R7 is substituted alkyl, wherein the substituent is aryl, and aryl is carboxyphenyl (note that carboxy is permitted under the definition of aryl as seen by page 27, lines 11-18; carboxy is on line 16).

(Alternatively, R7 is A_2 -aryl or A_2^- substituted aryl, leading to the same result).

Compounds 1 and 13 are the corresponding ester; these are covered – note page 137, lines 7-8. Compound 12 is similarly covered; note that the aminomethyl substituent is a permitted choice for a substituent on an aryl as seen by specification, page 27, line 15.

Compound 11 also anticipates. Note that this compound escapes the first proviso because it has B=phenyl, and escapes the second proviso because it has ACD as methylene. Ester compounds 15-16 and 21 also anticipate, this time with B=carboxyphenyl. The utility for all these species appears in the page 1693 Table. As the scope of claim 22 is unknown, it is included.

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Adlington (2001) has many of the same species. In addition, compounds with X1 = benzoyl (i.e. R7 in X1 as phenyl) are seen in table 2, compound 2; Table 5 compound 17. In addition, species 14 in Table 4 corresponds to X1 as SO₂R7 where R7 is tolyl, i.e. a substituted aryl.

Claims 1-2, 6, 8, 10, are rejected under 35 U.S.C. 102(b) as being anticipated by EP 1099690 A1.

Note that the WIPO version has a publication date of 2/3/2000.

The 1-benzoyl I-31 on page 27 species corresponds to R1=R2=R3=D=H, zero total A groups (i.e. A=bond), B is phenyl, and X1 is C(O)R7, where R7 is phenyl. The I-33 species on the same page has R1 as SO₂Phenyl, and R7 is NR₅R₄, wherein R₅ is H and R₅ is -A₂- heteroaryl. A₂ is the propylene group. This heterocycle meets the definition of heteroaryl because heteroaryl is not required by the specification to be aromatic. Note that page 27, line 19 includes "partially saturated". The heterocyclic ring here is partially saturated, not fully, because the C-C bond in the ring is itself unsaturated (aromatic, actually). Benzo-fusion is permitted by lines 25-27.

Claims 1-4, 6, 8, 10, are rejected under 35 U.S.C. 102(b) as being anticipated by France et al..

See compound 2, which corresponds to R2=R3=D=H, zero total A groups (i.e. A=bond), R1=ethoxycarbonyl, or COOR7, or R1 is carboxy, ester thereof, B is phenyl, and X1 as SO₂R7 where R7 is tolyl, i.e. a substituted aryl.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 6, 8-10, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP232017.

See Page 46, structure E-7 for the generic formula. A specific example is example 85 on page 34. This corresponds to $R_1=R_2=R_3=D=H$, A=methylene, B is heteroaryl (the triazole), substituted by two carboxy groups (permitted by specification page 27, line 30), in the ester form thereof, and X1 is C(O)R7, where R7 is pentyl. The sole difference is that the compound has an extra methyl group, i.e. having R61 (in structure E-7) as methyl; applicants have H at that position. However, R61 can be alternatively H, as is taught by page 8, line 32, and hence this is an obvious variation. It is also a homolog. Compounds that differ only by the presence or absence of an extra methyl group or two are homologues. Homologues are of such close structural similarity that the disclosure of a compound renders *prima facie* obvious its homologue. As was stated in *In re Grose*, 201 USPQ 57, 63, "The known structural relationship between adjacent homologues, for example, supplies a chemical theory upon which a *prima facie* case of obviousness of a compound may rest." The homologue is expected to be preparable by the same method and to have generally the same properties. This expectation is then deemed the motivation for preparing homologues. Of course, these presumptions are rebuttable by the showing of unexpected effects, but initially, the homologues are obvious even in the absence of a specific teaching to add or remove methyl groups. See *In re Wood*, 199 USPQ 137; *In re Hoke*, 195 USPQ

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148; *In re Lohr*, 137 USPQ 548; *In re Magerlein*, 202 USPQ 473; *In re Wiechert*, 152 USPQ 249; *Ex parte Henkel*, 130 USPQ 474; *In re Jones*, 74 USPQ 152, 154; *Ex Parte Fischer* 96 USPQ 345; *In re Fauque*, 121 USPQ 425; *In re Druery*, 138 USPQ 39; *in re Bowers and Orr*, 149 USPQ 570. In all of these cases, the close structural similarity between two compounds differing by one or two methyl groups was itself sufficient show obviousness. Note also *In re Jones*, 21 USPQ2d 1942, which states at 1943 “Particular types or categories of structural similarity without more, have, in past cases, given rise to *prima facie* obviousness”; one of those listed is “adjacent homologues and structural isomers”. Similar is *In re Schechter and LaForge*, 98 USPQ 144, 150, which states “a novel useful chemical compound which is homologous or isomeric with compounds of the prior art is unpatentable unless it possesses some unobvious or unexpected beneficial property not possessed by the prior art compounds.” Note also *In re Deuel* 34 USPQ2d 1210, 1214 which states, “Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties.” See also MPEP 2144.09, second paragraph.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

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The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- 1. What is meant by “linear string”? How could a string of these variables be anything but linear?**
- 2. $A^5 \cdot A^8$, unlike the other choices, are written as monovalent. This is incorrect; these are divalent.**
- 3. The term “the total number of linear A group is 0 to 6” does not make sense. The Formula clearly shows that there is exactly one A present.**
- 4. In proviso (a), the second and third R20 choices make no sense, as these were never permitted in the first place.**
- 5. The second and third choice for B in claim 1 are identical. One of them should be “alkylamino”.**
- 6. The first line of the (a) proviso appears to have a stray parenthesis.**
- 7. In proviso (b), the first “and” should be “then”.**
- 8. Choice (5) in proviso (b) is in error, as ACD cannot be that in the first place.**
- 9. The first material in parenthesis in claim 8 does not make sense; presumably it should be removed. If it is intended as a separate choice, the parenthesis should be removed and it should have a comma after it. For toher choice in parenthesis, it is not clear why parenthesis are used.**

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10. The second choice in claim 9 is of unknown meaning. What is this? The specification defines no such choice.
11. The next to last claim 9 choice for B is not provided for in claim 1. The specification does not teach that this is a choice and it should be deleted.
12. The claim 11 formula for X1 is missing its Y. Likewise claim 13.
13. The last B choice in claim 14 is not permitted by claim 1. B can be alkyl amino which is substituted on the alkyl, but this is not on the approved list of substituents on page 26, lines 18-22. The examiner is assuming in this regard that the line to the right is a methyl group, since the N at the left has only two bonds and hence must be the atom of attachment. If not, applicants need to add a second H onto the N.
14. A similar problem occurs in the 4th from last structure in claim 15. As written, it has a dangling valence at the left.
15. Claim 16, second choice for X1, gives a choice which does not appear in claim 1. that is, no Y choice in claim 1 will provide for a C(O)C(O)R25 group.
16. Similarly, most of the claim 17-19 choices for R25 do not correspond to anything provided for by claim 1. How, for example, would the last page 145 choice arise from claim 1?
17. In claim 16, what exactly are these "3 or more atoms" in R25? Is there an upper limit on how many there can be?
18. Claim 17-19 provide monovalent choice for R25, but R25 is a divalent radical, and hence it is not clear where the second bond is supposed to be.
19. The 9th and 11th claim 20 structure are misdrawn because atoms are overlapped. These must be draw clearly.

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20. N atoms must be shown with H atoms attached if the H atom is in fact present.

Applicants have omitted these on the piperidine rings in claim 20 species.

Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

There is no way of knowing which disorders are covered by this claim. There is simply not enough known about them. This covers disorders which are caused by too much, as well as too little, trypsin, tryptase, etc., as well as disorders which happen to cause the body to produce too much, as well as too little, trypsin, tryptase, etc.

Claims 1-19, 21-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for other forms, does not reasonably provide enablement for solvates. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims, insofar as they embrace solvates are not enabled. The evidence of the specification is clear: These compounds do not possess the property of forming solvates; there is no evidence that such compounds even exist.

The claims are drawn to solvates. But the more than 100 examples presented all failed to produce a solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no

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evidence that such compounds even exist.” The same circumstance appears to be true here: there is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

Claim 22 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Such scope cannot possibly be deemed to be enabled.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is “undue”; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds. Because of the staggering scope of the variables, trillions of compounds are embraced.

(b) Scope of the diseases covered. As set forth above, the scope of disorders here is unknown. The specification at pages 42-43 lists dozens of disorders, but, except for asthma,

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these are only raised as possibilities. Thus, page 42, lines 4 and 17, only say, May also be useful” and page 43, lines 2 and 11 say “may be useful”. Thus, the claim may cover these disorders, and then again, it may not.

(2) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that “the scope of enablement varies inversely with the degree of unpredictability of the factors involved,” and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is very limited. The dosage range information on page 45 gives a 50 fold dosage range, but, this is generic, the same for the many disorders covered by the specification. Thus, there is no specific direction or guidance regarding a regimen or dosage effective specifically for this or that disorder.

(4) State of the Prior Art: These compounds are N-acylated azetidinones with a particular substitution pattern at the 3- and 4-positions. So far as the examiner is aware, no of any kind have been used for the treatment of stroke, IBS, IBD, tumor growth, TIAs, DVT, psoriasis, etc, just to name a few of the page 42 disorders.

(5) Working Examples: There are none. In fact, no biological data of any kind is presented.

(6) Skill of those in the art: This is unknown, since, as noted above, it is unclear what art is involved.

(7) The quantity of experimentation needed: Owing to the above, especially factors 1), 3), 4) and 5), the quantity is expected to be high.

MPEP 2164.01(a) states, “A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the

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application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).” That conclusion is clearly justified here.

Claim 23 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Except for factor 1b and factor 6, the same applies here as well. And note the following:

A. The claim covers the prevention of asthma. The MDAdvice.com entry for Asthma <http://www.mdadvice.com/topics/asthma/info/1.htm> downloaded from the Internet 3/5/03 says for prevention that, “Asthma cannot be prevented.” There are of course many drugs to treat asthma, but these do not prevent a person from having asthma. In other words, the skill level in the art of preventing asthma is essentially zero.

B. The specification does not actual say that the compounds are effective against allergic rhinitis. Page 42 only says that it “may also be useful” for this. As was stated in *Ex parte Bhide* 42 USPQ2d 1441 (1/31/1996), “one skilled in the art would understand the “may be useful” and “may also act as inhibitors” statements to be possibilities -- not actual statements of use.”

Claim Objections

Claim 20 must end with a period.

Specification

The abstract is objected to as too vague. The definition of the capping group B should be added.

The structures with atoms obscured should be redrawn, especially for examples 139, 130 and 163.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Mark L. Berch
Primary Examiner
Art Unit 1624

12/8/05